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SOME RECENT STUDIES IN THE CARDIOTOXICITY OF AEROSOL PROPELLANT--ETC(U)
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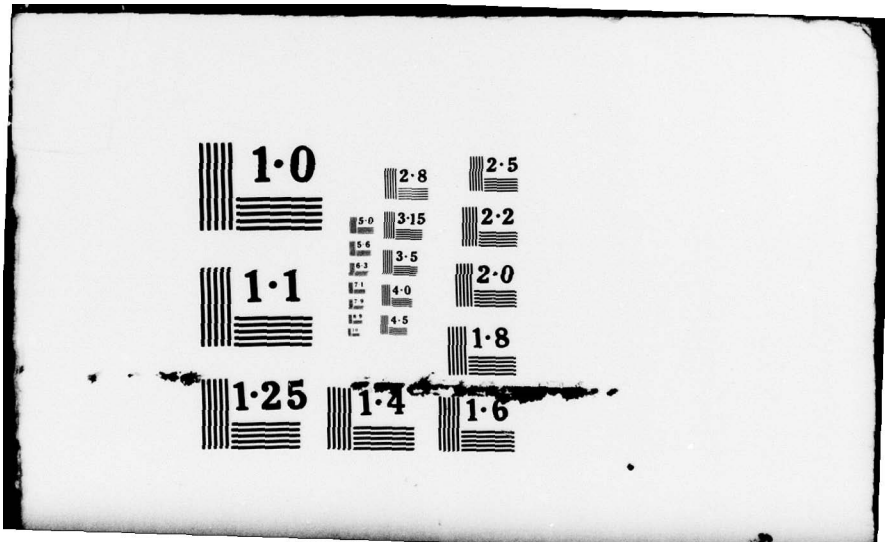
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by

Zijad Durakovic, Luka Stilinovic, et al.

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SOME RECENT STUDIES IN THE CARDIOTOXICITY OF AEROSOL PROPELLANTS

Zijad Durakovic[1], Luka Stilinovic[2], Ivan Bakran Jr.[3], and Senadin Durakovic[4]

The chlorofluoromethane and ethane derivatives, because of their exceptional physio-chemical properties are very often used as propellant gas for different materials which are to be dispersed as aerosols (different household sprays, cosmetic sprays, medicines for inhalation, etc). The same gases are used as cooling gases in refrigeration equipment because they have a very low conversion point from liquid to gas and so the gas cools the environment. On the market, they have the names: Arcton, Genotron, Isotron, Frigen, Forane, Algoforane, Freon, etc. Manufacturer's advertising claims that such gases are practically non-toxic, do not irritate the respiratory organs and do not smell even at a 20% concentration volume in the air.[1] Such a claim is based on the chemical stability of the methane and ethane derivitives because of the stable chemical connection among the fluorine, chlorine and carbon, and on the basis of experiments with animals.[2]

The cardiotoxicity of the propellant gases has been the subject of studies in the U.S.A. since 1970 after the publication of the expidemiological study about the sudden and unexpected deaths among youngsters using different aerosols[3].

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Two years before, Speizer et al., had observed a high death rate among asthmatics who over-used and used uncontrolled (by inhalation) imprenaline aerosol. Since then, this type of medicine has been obtainable only by prescription in Great Britian[3]. In our country (Yugoslavia), in 1974 an extensive article was published about this problem[6]. We can say about these initial studies that some researchers believe that propellant gases sensitize the heart on the arrhythmic action of the endogenic catecholamines[3,7,8]. Some researchers believe that the inhalation of propellant gases causes arrhythmia because of asphyxia[9-11] and others claim a cardiotoxic effect[13-16].

In 1972 we published an article on the arrhythmogenic effect of the dichlorofluoromethane on a rat heart (Arcon 12, Freon 12)[16]. At the time we published our article, only one experimental study by Taylor, Harris[9] and Silvergradeova[11] had been published which was critical of our study. From the theoretical and practical point of view the problem is important today. We will try to study the problem on the basis of our own experimental research with animals and on the basis of the studies of other authors. The latest experimental studies contribute much to the understanding of the damaging mechanism of propellant gases, but we must say, there is still a lot of discrepancy in the interpretation of the arrhythmogenic effect. Cohen[17] believes that the inhalation of different aerosols with propellant gases causes a respiratory depression, tachycardia, and pupil dilation; and that clinical patterns are the same as those for delirium or mental unbalance. He believes that, in the case of overuse of the spray, death occurs because of respiratory cardiac arrest. However, it is not possible to learn from the article if the author is talking about the effect of the active substance or the toxic effect of the propellant gas. The author blames the propellant gas for the larynx cooling and spasm. Only one component of the aerosol - the propellant gas - has the capability of evaporation point. Thus, the effect is cooling of the environment.

Bass[3] questions such an explanation of the propellant gas effect. He believes that the persons who have died suddenly inhaling the propellant gas did not inhale the cold gas. Thus, cooling of the larynx was impossible, because the propellant gas reaches the larynx as a gas already warm. Bass[3] adds that death occurs very fast, so it cannot be explained by progressive brain damage. Cohen[17] believes that the sudden death occurs after the aerosol inhalation because of the heart arrhythmia caused by hypoxia. Our research shows that the rat's asphyxia causes only a transient bradycardia[16]. Taylor[18] has tried to explain the importance of hypoxia for the heart arrhythmia occurrence in the case of Freon II. In his (Taylor's) experiments, rabbits have inhaled 9 possible mixtures of 21%, 11% or 7% oxygen with 0%, 5% or 15% of Freon II. Simultaneous inhalation of Freon II and oxygen has caused bradyarrhythemia, atrio-ventricular blockages and, finally, respiratory arrest in the experimental animals. This leads the author to conclude that changes of heart rhythms are caused as an interaction of hypoxia and Freon II on the transparent level of the heart muscle.

Unexplained mechanisms of the arrhythmogenic effect of propellant gases was a reason that Aviado and Belej[19] systematically tested 15 different propellants. After the intravenous anesthetization of mice by ternobarbiton, the experimental animals inhale propellants for 6 minutes. Some of the animals were given adrenalin intravenously. In accordance with the obtained results, the propellants were divided into three groups: the first group are propellants which cause heart arrhythmia and sensitize the heart for adrenaline effect (Freon 11, 3-chloromonofluoromethane, Freon 21, vinyl chloride, methylene chloride, trichloroethane and Freon 113 - trichlorotrifluoroethane); in the second group are the propellants which sensitize the heart for adrenaline (Freon 22, chlorodifluoromethane, Freon 114, dichlorotetrafluoroethane Freon 115, chloropentafluoroethane, octafluorocyclobutane, isobutane and propane); in the third group are propellants

which do not sensitize the heart for the adrenaline effect (Freon 12, dichlorofluoromethane, Freon 142b, monochlorodifluoroethane and Freon 152a difluoroethane). The inhalation of Freon 11, 21 and 113 in a concentration of 10% has caused atrioventricular blockage and ventricular extrasistole. The gases from the second group did not cause heart arrhythmia even in concentrations of 40% to 60%. In our experiments[16], Freon 12, after 1-1.5 minutes of inhalation by rats, has caused disturbances of the rhythm and the flow (nodal rhythm, ventricular extrasistole, all kinds of blockages, up to the total atrioventricular blockage), and finally, an astole after 8 to 30 minutes from the beginning of the inhalation. This is the difference between our experiments and Avaid and Beley experiments. It seems to us that the differences are caused by the different types of experimental animals and different concentrations of Freon 12. This claim was confirmed by the results of Reinhardt et al.[20]. They did test the effect of 13 propellant gases on the dog heart. All tested propelant gases, including Freon 12, have caused arrhythmia. Another important variable in the experiments is the difference in the concentration of the propellant gas and the duration of inhalation. In our experiments, rats have inhaled Freon 12 in concentrations higher than 60% for 1-1.5 minutes. The mice[19] were exposed to the same gas for 6 minutes and the concentration was higher than 40%. Finally, the dogs[20] have inhaled the same gas for 5 minutes in concentrations of 2.5% to 5%.

In our newest study[21], we have tested (using the same method) the influence of Freon 114 (dichlorotetrafluoroethane) on the rat heart. The animals have inhaled propellant gas from a plastic bag for 1-1.5 minutes. Immediately after inhalation stops, sinoatric blockage, atrioventricular blockages of the second order type Mobitz I and Mobitz II have occured, further consequences have been complete atrio-ventricular blockage, progressive bradyarrhythmia, microvoltage and cardiac arrest. These results are almost identical to the arrhythmias caused by Freon 12 in our previous experiments.

Beley et al.[22] have tested the influence of 15 propellant gases on monkey hearts. The monkies have been anesthesized using fenobarbitone. The experimental animals were artificially ventilated during the test and propellant gases were inhaled for 10 minutes in concentrations of 0.5%, 1%, 2.5% and 5%. After inhalation the adrenaline infusion was done for 5 minutes with a dose of 5 mcg/kg/min. and inhalation of the propellant gas. Freon 11 in concentrations of 2.5% did not cause changes, but 5% Freon 11 has caused ventricular extrasistole and atrioventricular blockage in 2 of 7 monkies. The combination of miocardiac ischemia caused by adrenergic adrenaline stimulation has increased heart sensitivity for arrhythmogenic action of *Freon 11 tenfold*. We have to mention the interesting study of Aviado and Belej[23] of the isolated dog heart that has shown the depression of the heart chamber function for concentrations of inhaled Freon 11 and 113 of 2.5% and 5%. Freons C-318, 115 and 152a have caused the decrease of the miocardio contractibility in concentrations of 10% and 20%.

Doherty and Aviado[24] have studied the adrenaline role in heart arrhythmia after the inhalation of propellant gases. They have tested the effect of Freon 11, 12 and 152a on adrenalektomized rats. For adrenalektomized animals, Freon 11 in concentrations of 20% and Freon 12 in concentrations of 40% have caused arrhythmia. In the control group of experimental animals with intact thyroid gland, concentrations of Freon 11 and 12 twice as small, caused heart arrhythmia. The electrocardiogram changes caused by Freon 152a were similar to changes after inhalation of Freon 12 for adrenalektomized animals and for control group animals. These facts led them to the conclusion that all three propellant gases cause arrhythmia indirectly because of the secretion of katcholamina from the thyroid glands and by the direct stimulation of the beta-adenergic receptors of the miocard. The same effect of propellant gas on the heart was achieved by the absence of arrhythmia after the blockage of the beta-adrenergic receptors using sotalole and propranolole. As a most important result, Doerrty and Aviado

consider the fact that some propellant gases do not cause heart arrhythmia in mice and monkeys, but do cause abnormality in the electrocardiograms of rats. All of the tested propellant gases cause a heart arrhythmia in at least one type of animal (mice, rats, monkeys). This means that all of the gases are arrhythmogenic and rats are most sensitive to their arrhythmogenic action.

Kilen and Harris[25] have tested under in vitro condition the contractual capability of the isolated papilar muscle of the left rat heart chamber. Freon 12 in concentration of 11.35 mg/100 ml, rapidly decreased reversible isometric contraction of the papilar muscle. The effect of Freon 12 depends on the dose, for example, 1.06 mg/100 ml caused the decrease of the isometric contraction for about 20%. The negative isotropic effect of Freon 12 occured regardless of the quantity of available oxygen. Therefore, the depression of the contractibility of the miocardium could be a cause for sudden and unexpected death of children using the propellant gases as a drug.

Friedman et al.[26] have determined the lethal concentration of the seven propellant gases for rats. All tested propellant gasses (Freon 11, 12, 21, 114, C-138 and isobutane) have caused apnea and finally, cardiac arrest. The fastest was Freon 21. It caused the apnea after four minutes of inhalation in concentrations of 19%. Freon C-318 was the slowest; it caused apnea after 26 minutes in concentrations of 48%. The electrical activity of the heart disappears in 5 to 10 minutes from the occurance of the apnea. Before apnea it was noticed that the transitory acceleration of breathing had occured. The transitory acceleration of breathing, the decrease of breathing volume and the increased resistivity in the respiratory paths were noticed, but the authors did not try to explain them. Our results are very similar[21], but the speed of the apnea appearance depended on dosage. When the animals inhaled propellant gas Freon 114 for one minute, the apnea appeared in 2 to 10 minutes from the end of inhalation. When the animals inhaled for 1.5 minutes, the apnea appeared one to three minutes after inhalation.

Friedman et al.[26] have divided the propellant gases into three groups with respect to their effect on lung function. In the first group are Freon 12 and 21 which do not cause an increase of bronchial resistivity; in the second group are Freon 11 and C-318 which decrease lung elasticity and breathing volume; in the third group are Freon 114 and 115 which cause tehypney. On the basis of these results, Friedman et al. recommend that the two most toxic propellant gases Freon 11 and 12 be replaced with other less toxic propellant gases in aerosol cans. Brody et al.[27] have tested the effect of Freon 11, 12 and 152a on the heart and lung in 96 mice. The mice have inhaled the propellant gases for 4 minutes in concentrations of 1% and 2%. This relatively low concentration of propellant gas causes an increase of the bronchial resistivity and decrease of lung elasticity. Intratrachial application of papain has caused the decrease of breathing frequency and consecutively a decrease of the minute lung ventilation, but breathing volume does not change. Lung edema was found post-mortem. Further, in experimentation, the animals with lung damage using the proteolytic enzyme of the papain have inhaled propellant gas for 4 minutes. This decreases the breathing volume, minute lung ventilation, lung elasticity and breathing frequency. Seven minutes after inhalation of 10%-Freon 11 we have a heart arrhythmia for 4 minutes. Intravenous application of adrenaline accelerates the occurance of arrhythmia, for example, arrhythmia appears for 3.8 minutes after the inhalation of the propellant gas. For experimental animals with preliminary given papain, 10% Freon 11 has caused large disturbances of rhythm and behavior regardless of the adrenalin. The inhalation of Freon 12 for 4 minutes in concentrations of 40% together with adrenaline has produced a high amplitude of the ARS complex of the electrocardiogram. Freon 152a caused arrhythmia but combination with adrenaline did not increase the arrhythmogenic effect of the propellant gas in mice pretreated with papain. The conclusion is that death is the result of cardiac arrest.

Measuring the chemodynamic changes for dogs, Simaan and Aviado[28] have tried to test the direct effect of Freon on the dog heart. They have recorded the pressure in the lung artery, left atrium and in the left chamber at the end of the diastole. The dogs inhaled Freon 11, 12, 114, 152a and C-318. A concentration of Freon 11 of 0.5% did not cause pressure changes, but 1% Freon 11 did cause an important pressure decrease and an increase of heart frequency and pulmonary vascular resistivity. Freon 12 caused the same effect, but in concentration of 10%, Freon 114 in concentration in concentration of 2.5%, Freon 318 in concentration of 20% and Freon 152a did not have any effect in concentration of 20%. It is important to say that the system vascular resistivity was not stable during the experiment; increasing and decreasing, in an amount causing the authors to conclude that its measurement is not important for the experiments. In their latest study, Simaan and Aviado[29] have perfused isolated dog lungs and then applied propellant gas by inhalation. Freon 11, 12 and 114 have caused a drop of the average aorta pressure but only Freon 11 and 14 have decreased pressure in the lung artery. When the animals have obtained, together with Freon, the blocator of the alfa-adrenergic receptors, the average pressure in the lung artery, in the aorta and the average perfusion pressure decreased. The pressure in the left atrium and the heart frequency did not change. In order to find out if the propellant gas acts locally on the parasymptotic reflex mechanism of the respiratory system, parasympaticolitic atropin was administered to the animals. The inhalation of 5% Freon 11 after atropin had the same effect as in the experiment with tentolamin - alfa-adrenergic blocator.

Finally, we would like to mention the case of a 16 year old who has died, probably because of the inhalation of an overdose of aerosol from a plastic bag.[30] It was a mixture of Freon 11 and 12. The epidemologic data about the inhalation of propellang gas are confirmed, and an hour after inhalation he died in the local hospital. Postmortem analysis using gas chromatography was applied to measure the concentration of Freon 11 and 12 in different times. Propellang gases were found

Figure 1. Wright "air peak flow meter"

in the blood, brain, liver, kidney, larynx and bladder. The author concluded that such a distribution is similar to the distibution of chloroform after death caused by chloroform. It appears that such a good postmortem analysis has proven that for humans there is a danger in the case of over-inhalation, if not of all propellant gases, at least for Freon 11 and 12. To this time, cardiotoxic concentrations of the particular propellant gas, the precise mechanisms of its action and different sensitivity of different animals on the inhalation of the propellant gases is an open question.

Our personal experiences give us enough reasons to consider an indispensible rational approach to the application of the bronchospasmolics in the form of an aerosol. It is necessary to know about the danger from the arrhythmogenic effect of the propellant gas and bring it to the patients' attention. On the other hand, a bronchospasmolitic of the sympaticomimetic type should be prescribed only in the case when, on the basis of functional testing of the lungs, we come to the conclusion that the bronchial obstruction of the patient at the given moment is only or basically, caused by the spasm of the smooth bronchial muscle and has a reversible character. It is hopeless to

expect results from such medicine in the case of inflamation of nasal passages and the obstruction of the respiratory paths with high viscosity spasm. Probably, such circumstances force the lung patient to uncontrolled use and in panic because of short breath, he continues to inhale the bronchospasmatic, exposing himself to danger.

All these remarks do not intend to discredit this important and useful group of medicines, but only to create an appropriate therapeutic attitude toward their application.

It is impossible to evaluate the therapeutic effect of antihypertensor without measurement of the pressure. We have many prescriptions for bronchospasmolitics, most often in the form of aerosol, without evaluation of their therapeutic effect. If the evaluation of their therapeutic effect is done, then it is based on a patient's statement or on the basis of lung ascultation. Today, we have instruments, no more expensive than a pressure meter, which can evaluate the effect of the bronchospasmolitics very quickly. The Wright peak flow meter is such an instrument. Such an instrument can help to evaluate the effect of the bronchospasmolitic and its therapeutic action. Using the graph of the normalized value we can scale the effect of the bronchospasmolitic. We believe that by using such an instrument, lung patients can protect themselves from the harmful effects of aerosols and propellant gases of the bronchospasmolitic. The lung patient should know that if, after the use of the bronchospasmolitic, he does not feel better, he should immediately contact his physician. Only the physician can diagnose the right reason and the treatment and if the patient has inhaled a large quantity of bronchospasmolitic, the physician may decide to use corticosteroide.

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